REMARKS

Status of the Claims

Claims 25-29 and 35-44 are pending and claims 35-44 are under consideration in this application, claims 1-24 and 30-34 having been cancelled and claims 25-29 having been withdrawn for allegedly being drawn to separate inventions. All the claims under consideration stand rejected. After entry of the amendments made in this application, claims 25-29, 43, and 45-47 will be pending and claims 43 and 45-47 will be under consideration in this application, new claims 45 - 47 having been added and claims 35-42 and 44 having been cancelled without prejudice to their being presented in a separate application or to embodiments specified by them being added to other pending claims or included in claims to be added in the present application.

New claims 45 and 46 are supported throughout the specification. For the convenience of the Examiner, claims 45 and 46 are recited below with examples of textual support in the specification for various claim terms indicated in parentheses after the terms.

45. (New) A method to increase neurite regeneration (page 19, line 8) in the CNS in a patient with a traumatic spinal cord lesion (page 19, line 10) following spinal cord damage (page 14, line 21), the method comprising

delivering to a nerve growth environment (page 6, line 8) by infusion into a site of surgery for said spinal cord lesion (page 19, line 28), a Rho family antagonist in an amount effective to suppress inhibition of neuronal axon growth,

which antagonist ribosylates Rho protein family members to inactivate said Rho family members (page 11, lines 3-4), and

which antagonist, when scrape loaded into PC12 cells *in vitro*, produces outgrowth of PC12 cell neurites, said PC12 cells being plated on a growth inhibitory substrate selected from the group consisting of myelin and myelin-associated glycoprotein substrate,

said antagonist being a C3 ADP-ribosyl transferase.

46. (New) A method to increase neurite regeneration (page 19, line 8) in the CNS in a patient with a traumatic spinal cord lesion (page 19, line 10) following spinal cord damage (page 14, line 21), the method comprising

delivering to a nerve growth environment (page 6, line 8) by infusion into a site of surgery for said spinal cord lesion (page 19, line 28), a Rho family antagonist in an amount effective to suppress inhibition of neuronal axon growth,

which antagonist ribosylates Rho protein family members to inactivate said Rho family members (page 11, lines 3-4), and

which antagonist, when scrape loaded into PC12 cells *in vitro*, produces outgrowth of PC12 cell neurites, said PC12 cells being plated on a growth inhibitory substrate selected from the group consisting of myelin and myelin-associated glycoprotein substrate,

said antagonist being a Rho family-inhibitory fragment of (page 5, line 8) C3 ADP-ribosyl transferase.

Applicants point out that although the text on page 19, line 28, uses the word "operation", Applicants have used the corresponding word ("surgery") that is more common in U.S. usage.

Claim 43 has been made dependent on claim 35 and amended to conform its language to that used in claim 45. New claim 47, which is dependent on claim 46, corresponds to claim 43.

No new matter is added by the new claims or the amendment to claim 43.

Priority

From the comments on page 2, line 18, to page 3, line 8, of the Office Action, Applicants understand the Examiner's position to be that the instant application should not have the priority of the Canadian Patent Application No. 2,214,841 (the '841 application; filed October 31, 1997) because treatment of PC12 cells *in vitro* is not an art-accepted model for predicting *in vivo* neuronal growth. Applicants disagree with this position.

Applicants respectfully submit that those skilled in the art would conclude from the prior art references submitted with the Amendment and Response filed June 2, 2004 (Tomaselli et al, Rubin et al., and Daniels) that PC12 cells *in vitro* are subject to similar

growth-inhibitory influences that nerve cells are subject to *in vivo*. In this regard, while the statement on page 3, lines 11-13, of the '841 application specification quoted in the prior Amendment and Response is entirely correct, the scientific article referred to in support of the statement was incorrectly cited. Applicants apologize for this inadvertent error. The correct citation is: Lamoureux et al. (1997) J. Cell Sci. 110(Pt2);635-641. A copy of this article is enclosed together with the Information Disclosure Statement (IDS) filed herewith.

Applicants submit that, in view of the above teaching by the prior art, one skilled in the art would believe that factors that antagonize growth-inhibitory effects on PC12 cells *in vitro* would likely have similar growth-inhibition antagonizing effects on neurons *in vivo*. In addition, in view of the prior art described on pages 1-3 in the Background section of the '841 application, one skilled in the art would believe that Rho family growth inhibitors act on undamaged as well as damaged neurons. Such an artisan would conclude from all these teachings that the C3 ADP- ribosyl transferase that facilitated neurite outgrowth in PC12 cells *in vitro* (as shown by the data in Example I of the '841 application) would likely function on intact or damaged (e.g., traumatized) neurons *in vivo*.

In addition, while the '841 application does not contain actual *in vivo* data, it does contain an extensive description of *in vivo* methods (see, for example, page 10, paragraph 10, and page 17, last paragraph, to page 19, paragraph 2). In light of the *in vitro* data presented in the '841 application and the prior art (see above), skilled artisans in the field of neurology would expect that the *in vivo* the methods described in the document would likely be at least partial therapeutic benefit when performed alone or in combination with other therapeutic modalities. The *in vivo* data provided in the present application indicates that such expectations would have been correct.

With respect to the Crutcher reference, Applicants draw the Examiner's attention to the fact that, in addition to the advances in knowledge made between the reference's publication and the filing date of the '841 application (see Amendment and Response filed June 2, 2004), the subject matter of the '841 application and the instant application and differs substantially from that of Crutcher.

As pointed out on page 300 of Crutcher, the article deals only with nerve growth factors that meet the following criteria:

1. The agent exhibits an effect on neuronal growth or differentiation in vivo.. . .

2. The agent is normally available to the neurons it affects. A corollary to this is that the agent is normally present in vivo at the time its growth effect is manifested. . . .

3. Neurons affected by the agent contain specific membrane receptors for the growth factor. . . . It is possible that some of the putative growth factors exhibit effects in the absence of specific receptors . . . but the concept of specificity seems to require some type of receptor-ligand interaction."

While the growth inhibitor-antagonizing agents of the instant invention do act *in vivo* (and thus fulfill criterion 1), they are not "normally available to the neurons" they affect, and neurons affected by them do not "contain specific membrane receptors for the growth factor" (and thus do not fulfill criteria 2 and 3). Notably, Crutcher does not mention endogenous growth inhibitors at all, let alone Rho-family growth inhibitors. Moreover, it does not mention antagonists of endogenous growth inhibitors, let alone C3 ADP-ribosyl transferase. In light of these factors, Applicants respectfully submit that the disclosure of the Crutcher reference is not relevant to methods of the instant invention.

In that claims 35-42 and 44 have been cancelled, the comments on page 4, line 21, to page 5, line 5, of the Office Action are moot.

In view of all the above considerations, Applicants respectfully submit that instant application is entitled to the priority of the filing date of the '841 application i.e., October 31, 1997.

35 U.S.C. §112, first paragraph, rejections

(a) Claims 35-44 stand rejected as allegedly containing subjecr matter that was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventors, at the time the application was filed, had possession of the claimed invention.

From the comments on page 5, line 18, to page 6, line 2, of the Office Action, Applicants understand the Examiner's position to be that the term "in a nerve" is not supported by the specification. While the rejection is moot in view of the cancellation of claims 35-42 and 44, Applicants disagree with this position. Thus, in both the *in vitro* scrape loading experiment described in Example I (page 25) and the *in vivo* optic nerve crush

experiment described in Example II (pages 28 -30) of the instant specification, C3 ADP-ribosyl transferase (CART) was delivered "in a nerve". In light of these considerations, Applicants reserve the right to inlcude this limitation in new claims in the present application, in new claims to be added to the present application, or in the claims of a separate application.

From the comments on page 6, line 3, to page 7, line 19, Applicants understand the Examiner's position to be that the instant specification does not provide adequate written description of biologically active fragments of CART. Applicants respectfully disagree with this position.

While claims 35-42 and 44 have been cancelled (see above), new claim 46 also specifies certain fragments of CART. However, rather than biological activity, these fragments have "Rho family-inhibitory" activity and thus the comments in the Office Action in regard to "biological activity" are moot. Applicants submit, moreover, that since the amino acid sequence of CART was known at the priority date of the instant application (see, for example, Nemoto et al. (1991) J. Biol. Chem. 266:19312-19319, a copy of which is submitted in the IDS filed herewith), all possible fragments of CART would have been known to those skilled in the art at the priority date of the instant application. In addition, in that CART is a relatively small (23 kDa) protein, the total number of fragments to test would be relatively low. Moreover, given the information in regard to critical residues in CART described below, such an artisan would be able to drastically limit the range of fragments of CART likely to have Rho family-inhibitory activity. Having selected likely candidates, the artisan could then test them for such activity using the *in vitro* and/or and *in vivo* methods described in the instant specification (Examples I and II, respectively) or any other methods known in the art.

(b) Claims 35 -44 stand rejected on the grounds that the specification allegedly does not enable one skilled in the art to practice the invention commensurate in scope with these claims.

Applicants respectfully submit that the comments on page 8, lines 19-22, of the Office Action, are moot in light of the cancellation of claims 35 – 42 and 44 and the use of language in new claims 45 and 46 that makes it abundantly clear that the limitation corresponding to

that at issue ("which antagonist, when scrape loaded into PC12 cells *in vitro*, produces outgrowth of PC12 cell neurites, said PC12 cells being plated on a growth inhibitory substrate selected from the group consisting of myelin and myelin-associated glycoprotein substrate") limits only the antagonists and not a method step.

From the comments on page 9, line 4, to page 10, line 2, of the Office Action, Applicants understand the Examiner's position to be that, in view of the complexity in nerve regeneration and the variety of nerve injuries encompassed by the claims, the claims are not enabled by the specification. Applicants respectfully disagree with this position.

First, Applicants draw the Examiner's attention to the fact that new claims 45 and 46 refer only to central nervous system (CNS), in particular spinal cord, injuries and to infusing the antagonists to a site of surgery with a spinal cord lesion. Applicants point out that optic nerves are classified as nerves of the CNS and thus the crushed optic nerve experiment described in Example II is of direct relevance to claims 45 and 46.

In support of the rejection, the Examiner cites three scientific articles. It is noted that all of these articles are were written prior to the information disclosed in the present application being made public. Nevertheless, Applicants respectfully submit that two of the references actually provided cause for optimism in the field of nerve regeneration.

In that the Liuzzi et al. reference relates only to peripheral nerve regeneration, it is not relevant to new claims 45 and 46. Applicants point out that the Jackowski reference, while detailing the complexity of the system, ends on a note of optimism for the future of CNS regeneration (page 311, column 2, paragraph 2, to the end of the article). Of particular relevance to the instant claims, the article includes as a possible therapeutic approach the use of agents (i.e., antibodies) that would antagonize "neurite-growth inhibitory molecules present in CNS-meylin" (page 311, column 2, lines 6-9). In addition, while the Davies et al. reference opens with the statement quoted in the Office Action (page 9, lines 12-16) as to the then prevailing dogma concerning the impossibilty of regenerating CNS axons, the article concludes, based on experimental findings presented in the article, that the dogma was incorrect and that "the adult CNS environment can support regenerative growth from a type of adult neuron that has never before been shown to possess such a remarkable ability to regenerate its axon within adult CNS white matter" (page 683, column 1, paragraph 4).

From the comments on page 10, line 3, to page 11, line 10, of the Office Action, Applicants understand the Examiner's position to be that the specification provides insufficient guidance as to dosages (in particular, "the amount effective to suppress inhibition of neuronal axon growth") and routes and duration of administration. First, claims 45 and 46 do specify a particular route of administration ("infusion into a site of surgery for said spinal injury"), which those skilled in the would recognize as being particularly direct and thus most likely to be efficacious. Applicants submit, moreover, that given the teaching of the specification on both *in vitro* and *in vivo* methods of determining the effects of Rho-family antagonists on nerve regeneration (in Examples I and II, respectively), one skilled in the art would readily be able to determine the above-listed parameters by entirely routine experimentation. The Examiner is reminded that a considerable amount of experimentation is permissible, provided it is of a routine nature. Applicants also point out that the U.S. Supreme Court has held that in patents covering multiple embodiments of an aspect of an invention, it is unreasonable to expect the patentee to provide details, such as concentrations, of each embodiment. Thus, in *Minerals Separation, Ltd. v. Hyde*, 242 U.S. 261 (1916), the U.S. Supreme Court held, in discussing the adequacy of the disclosure of a froth flotation process of ore separation, that

> [e]qually untenable is the claim that the patent is invalid for the reason that the evidence shows that when different ores are treated preliminary tests must be made to determine the amount of oil and extent of agitation necessary in order to obtain best results. Such variation of treatment must be within the scope of the claims, and the certainty which the law requires in patents is not greater than is reasonable, having due regard to their subject matter. The composition of ores varies infinitely, each one presenting its special problem, and it is obviously impossible to specify in a patent the precise treatment which would be most successful and economical in each case. *Id.* at 270.

The Examiner cited *In re Colianni*, 561 F.2d 220 (CCPA 1977) in regard to the above to the lack of enablement of the above-listed parameters. Claims 45 and 46 differ from those at issue in *In re Colianni* in that, in the patent in the patent at issue in *In re Colianni*, the specification not only failed to disclose what was "sufficient ultrasonic energy" as used in the clause "sufficient ultrasonic energy by direct mechanical subcutaneous connection to the bone on at least one side of the fracture

therein to join the bone together at the fracture" (recited in claim 1), it failed to disclose how to determine this parameter. *Id.*, at 222.

From the comments on page 11, line 11, to page 12, line 7, of the Office Action, Applicants understand the Examiner's position to be that "biologically active fragments" of CART are not enabled by the specification. Applicants respectfully disagree with this position.

First, Applicants point out that in claim 46 such fragments are specified as "Rho family-inhibitory" (rather than "biologically active") fragments of CART. In view of the amino acid sequence of CART being known at the priority date of instant application (see above), the relatively small size of CART (see above), and teachings of the art in regard to regions of CART important for its activity (see below), Applicants respectfully submit that the number of fragments one of skill in the art would have to test, using for example the *in vitro* and/or *n vivo* methods described in Examples I and II, respectively, of the instant specification, to identify a reasonable number falling within the scope of the claims would be far from infinite. It is noted that there is no requirement that the specification and prior art teach ways of establishing all possible fragments falling within the scope of the claims.

Important in this regard are the following teachings: (a) CART ribosylates Rho to inactivate the protein (e.g., page 10, lines 4-5, of the instant specification); (b) CART stimulates axon growth (e.g., Example II of the instant specification; and (c) the teachings of the prior art reference Saito et al. [(1995) FEBS Letters, 371: 105-109 ("Identification of Glu^{173} as the critical amino acid residue for the ADP-ribosyltransferase activity of *Clostridium botulinum* C3 exoenzyme"), a copy of which is included with the IDS filed herewith] in regard to critical residues in CART. Thus, based on the teaching of Saito et al., one skilled in the art would include Glu^{173} (see, for example, the Abstract and page 106, column 2, paragraph 3, first sentence) in candidate fragments to screen for activity (using, for example, the assays described in Examples I and II of the instant specification). Moreover, she would likely test fragments with and with out Phe^{9} – Gly^{19} (see, for example, the Abstract and page 107, paragraph spanning columns 1 and 2).

In light of the above considerations, Applicants respectfully submit that the pending claims are both supported by adequate written description in the specification and are enabled by the specification and thus request that the rejections under 35 U.S.C. §112, first paragraph, be withdrawn.

35 U.S.C. §112, second paragraph, rejection

Claims 35-44 stand rejected as allegedly being indefinite for failing to particularly point out and distinctly claim the subject matter which Applicants regard as the invention.

Applicants respectfully submit that the rejections are moot in light of the cancellation of claims 35-44.

CONCLUSION

In summary, for the reasons set forth above, Applicants maintain that the pending claims patentably define the invention. Applicants request that the Examiner reconsider the rejections as set forth in the Office Action, and permit the pending claims to pass to allowance.

If the Examiner would like to discuss any of the issues raised in the Office Action, Applicants' undersigned representative can be reached at the telephone number listed below.

Enclosed is a request for an automatic extension of time and a check in payment of the extension in time. Please charge any other fees or make any credits to Deposit Account No. 06-1050, referencing Attorney Docket No. 12552-002001.

Respectfully submitted,

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